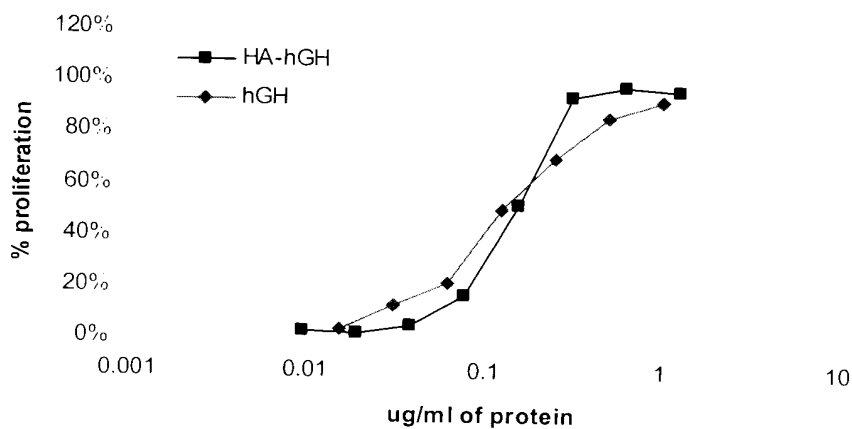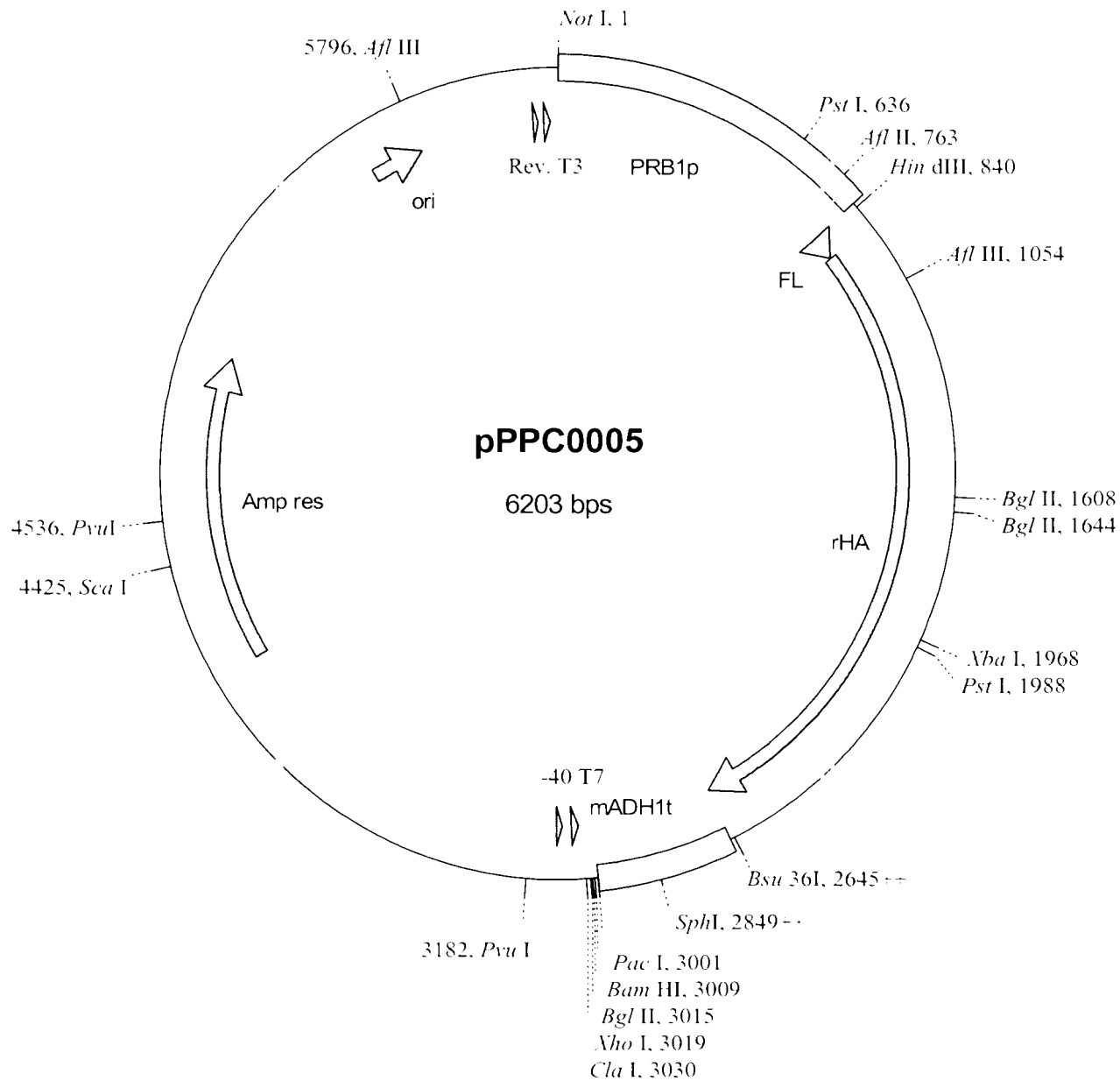**Figure 1**

Figure 2

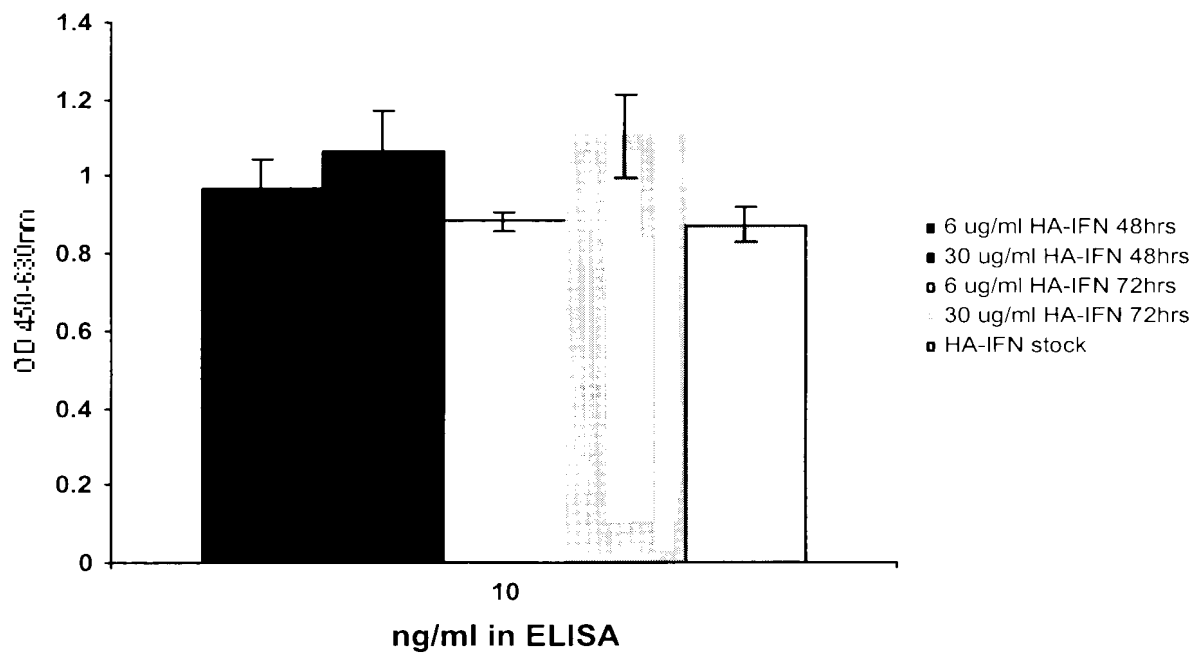**Figure 3A**

Figure 3B

Figure 4

Figure 5

Figure 6

Figure 7

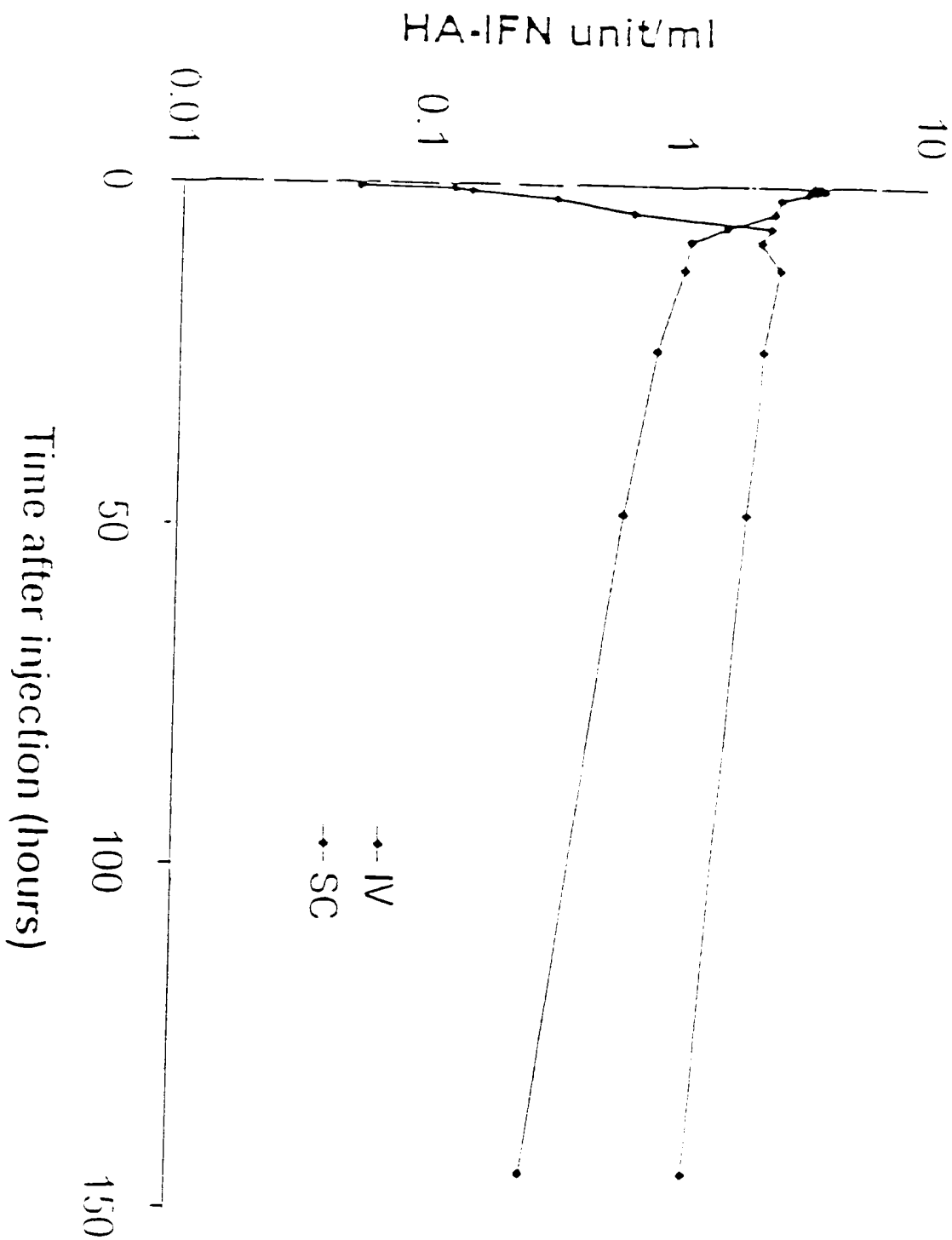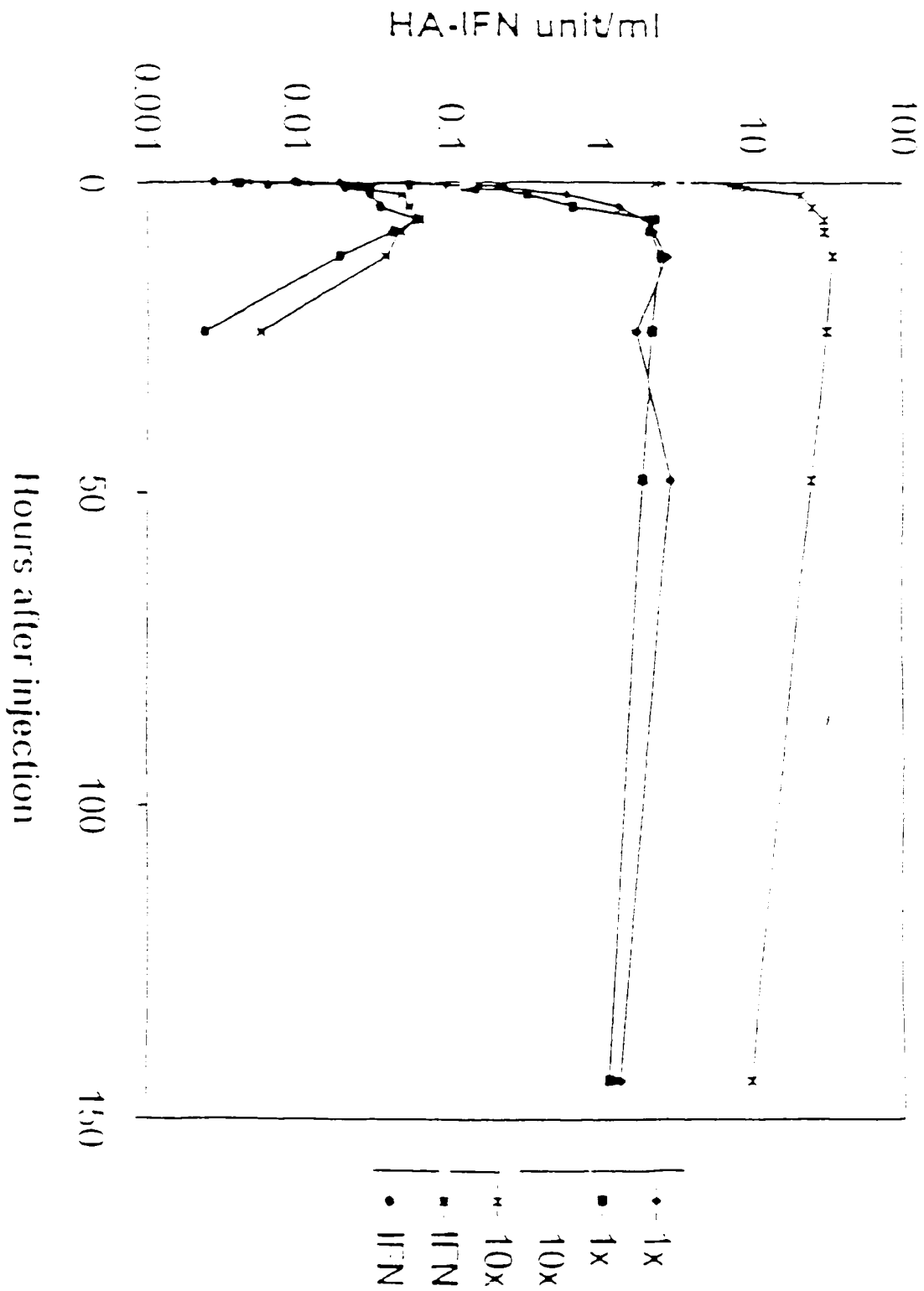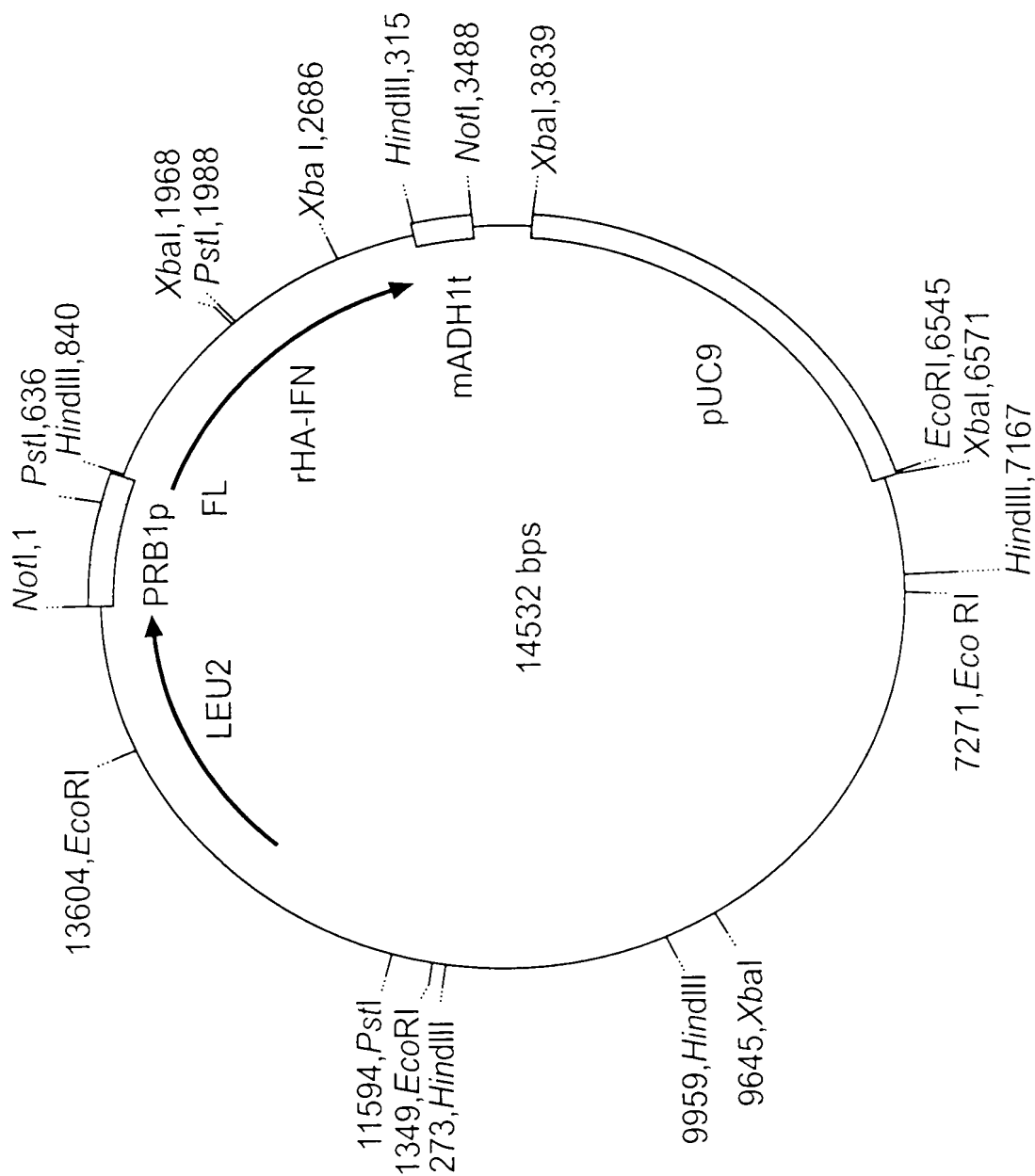*FIG. 8*

Figure 9

```
  1    DAHKSEVAHR FKDLGEENFK ALVLIAFAQY LQQCPFEDHV KLVNEVTEFA
         HHHHH HHH       HHH HHHHHHHHH      HHHHH HHHHHHHHH

                I                      II              III
 51    KTCVADESAE NCDKSLHTLF GDKLCTVATL RETYGEMADC CAKOEPERNE
         HHHHH               HHHHH HHHHH             HHHH H    HHHH

101    CFLQHKDDNP NLPRLVRPEV DVMCTAFHDN EETFLKKYLY EIARRHPYFY
         HHHH                H HHHHHHHH     HHHHHHHH HHHHH

                          IV
151    APELLFFAKR YKAAFTECCO AADKAACLLP KLDELRDEGK ASSAKQRLKC
         HHHHHHHHH HHHHHHHHH      HHHHH HHHEHHHHHH HHHHHHHHH

                                                       V
201    ASLQKFGERA FKAWAVARLS QRFPKAEFAE VSKLVTDLTK VHTECCHGDL
         HHHHH    HH HHHHHHHHH HH     HHH HHHHHHHHH HHHHHH  HH

                     VI         VII
251    LECADDRADL AKYICENODS ISSKLKECCE KPLLEKSHCI AEVENDEMPA
         HHHHHHHHH HHHHH           HHHHH    HHHHHHH H

301    DLPSLAADFV ESKDVCKNYA EAKDVFLGMF LYEYARRHPD YSVVLLLRLA
           HHHH      HHHHH     HHHHHHH HHHHHH       HHHHHHH

                VIII
351    KTYETTLEKC CAAADPHECY AKVFDEFKPL VEEPQNLIKQ NCELFEQLGE
         HHHHHHHHH      HH     H     HHHHH HHHHHHHHH HHHHHHH

                                                 IX
401    YKFQNALLVR YTKKVPQVST PTLVEVSFNL GKVGSKCCKH PEAKRMPCAE
         HHHHHHHHH HHHH        H HHHHHHHHH    HHH    HHHHHHH

                     X              XI
451    DYLSVVLNQL CVLHEKTPVS DRVTKCCTES LVNRRPPCFSA LEVDETYVPK
         HHHHHHHHH HHHHH      HHHHHHHHH    HHHHHHH

501    EFNAETFTFH ADICTLSEKE RCIKKQTALV ELVKHKPKAT KEQLKAVMDD
                    HHH      HHH HHHHMMEHHH HHH            HHHHHHHH

                XII
551    FAAFVEKCCK ADDKETCFAE EGKKLVAASQ AALGL
         HHHHHHH           HHHH HHHHHHHHHH HH
```

```
      Loop                      Loop
      I     Val54-Asn61         VII   Glu280-His288
      II    Thr76-Asp89         VIII  Ala362-Glu368
      III   Ala92-Glu100        IX    Lys439-Pro447
      IV    Gln170-Ala176       X     Val462-Lys475
      V     His247-Glu252       XI    Thr478-Pro486
      VI    Glu266-Glu277       XII   Lys560-Thr566
```

Figure 10

a. Randomisation of Loop IV.

```
                                    IV
    151    APELLFFAKR YKAAFTECCQ AADKAACLLP KLDELRDEGK ASSAKQRLKC
           HHHHHHHHHH HHHHHHHHH       HHHHH HHHHHHHHHH HHHHHHHHHH

                                    IV
    151    APELLFFAKR YKAAFTECCX XXXXXXCLLP KLDELRDEGK ASSAKQRLKC
           HHHHHHHHHH HHHHHHHHH       HHHHH HHHHHHHHHH HHHHHHHHHH
```

X represents the mutation of the natural amino acid to any other amino acid. One, more or all of the amino acids can be changed in this manner. This figure indicates all the residues have been changed.

b. Insertion (or replacement) of Randomised sequence into Loop IV.

```
                          (X) n
                            │
                            ▼

                                    IV
    151    APELLFFAKR YKAAFTECCQ AADKAACLLP KLDELRDEGK ASSAKQRLKC
           HHHHHHHHHH HHHHHHHHH       HHHHH HHHHHHHHHH HHHHHHHHHH
```

The insertion can be at any point on the loop and a length where n would typically be 6, 8, 12, 20 or 25.

FIG. 11A

FIG. 11B

APN: 09/832,501 (13 of 20)
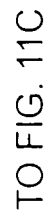David J. Ballance et al.
Atty. Docket: 6832.0012-00

13/20

FROM FIG. 11B

FROM FIG. 11B

DOMAIN 3

FIG. 11C

HOOC-

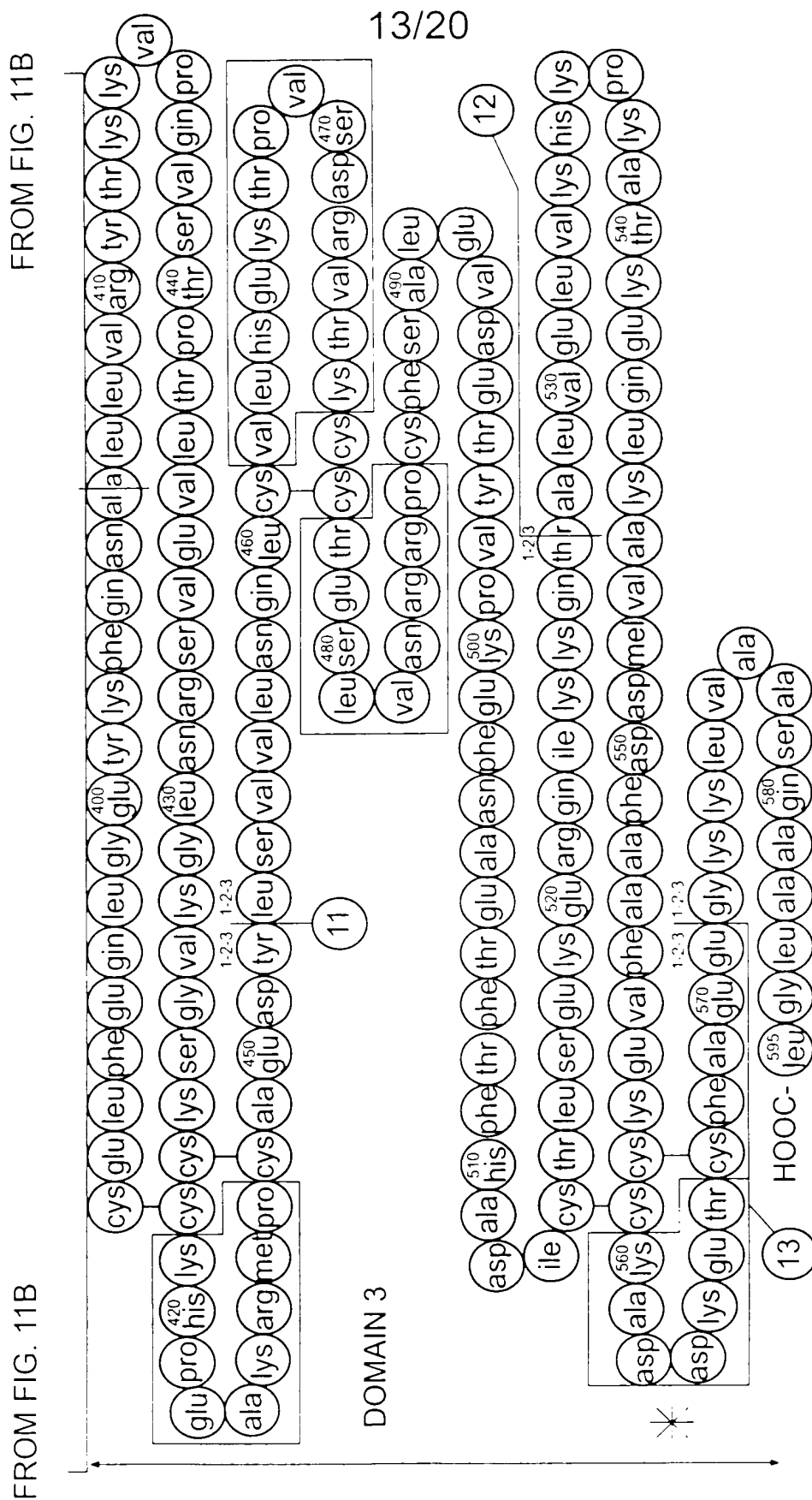= YELLOW

DISULFIDE BONDS SHOWN IN YELLOW
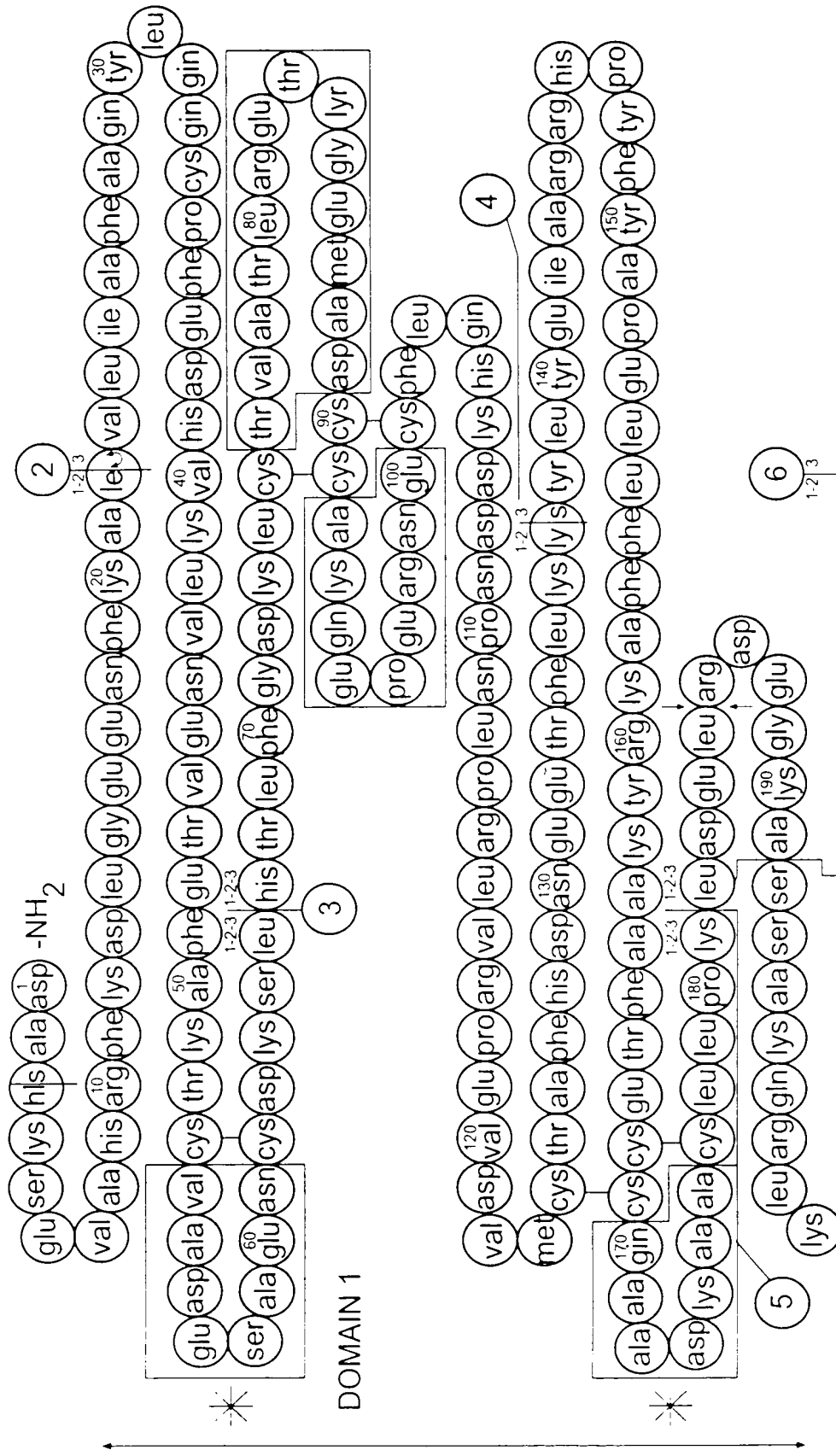
FIG. 12:
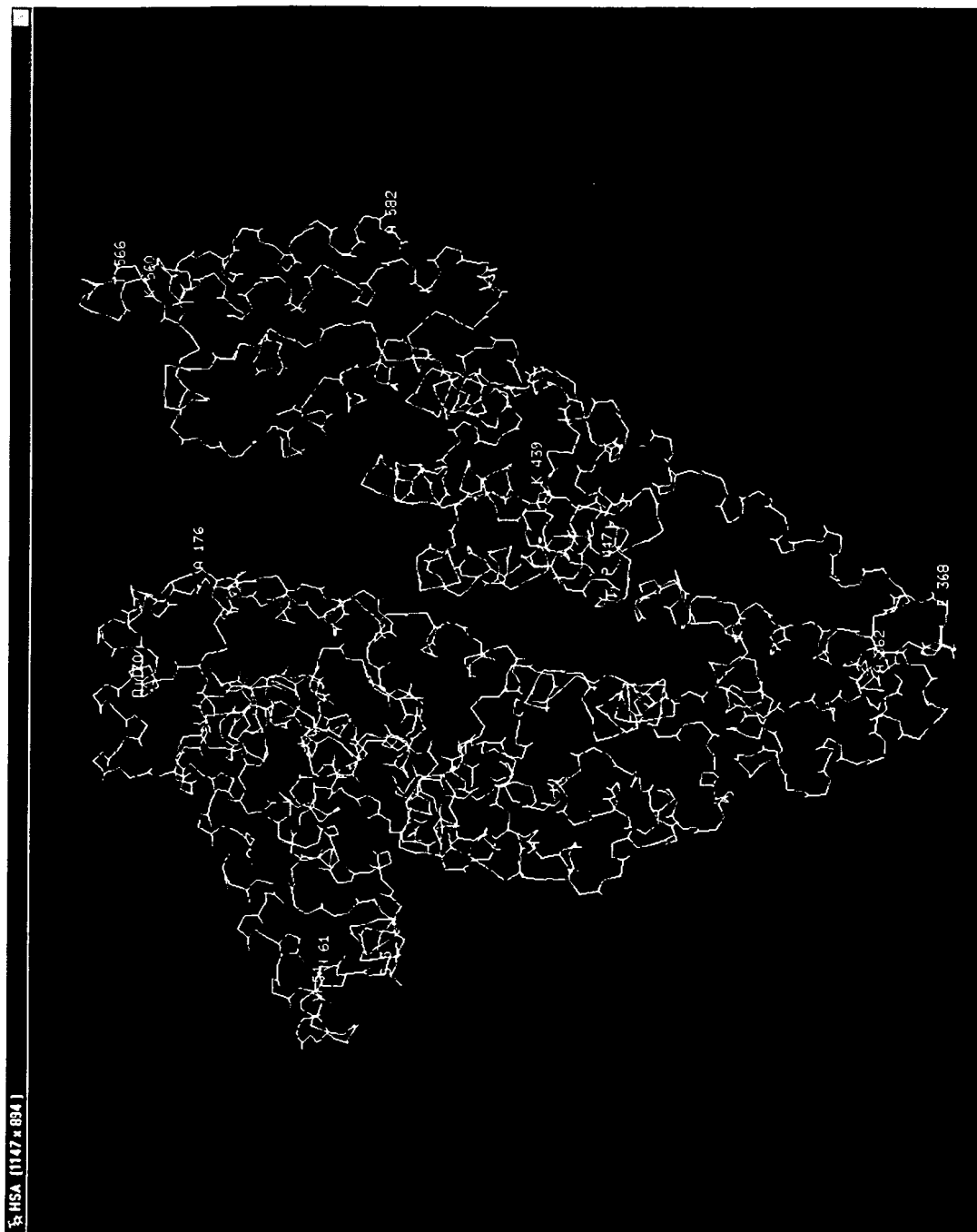*LOOP IV GLU170-A176*

FIG. 13
TERTIARY STRUCTURE OF HA

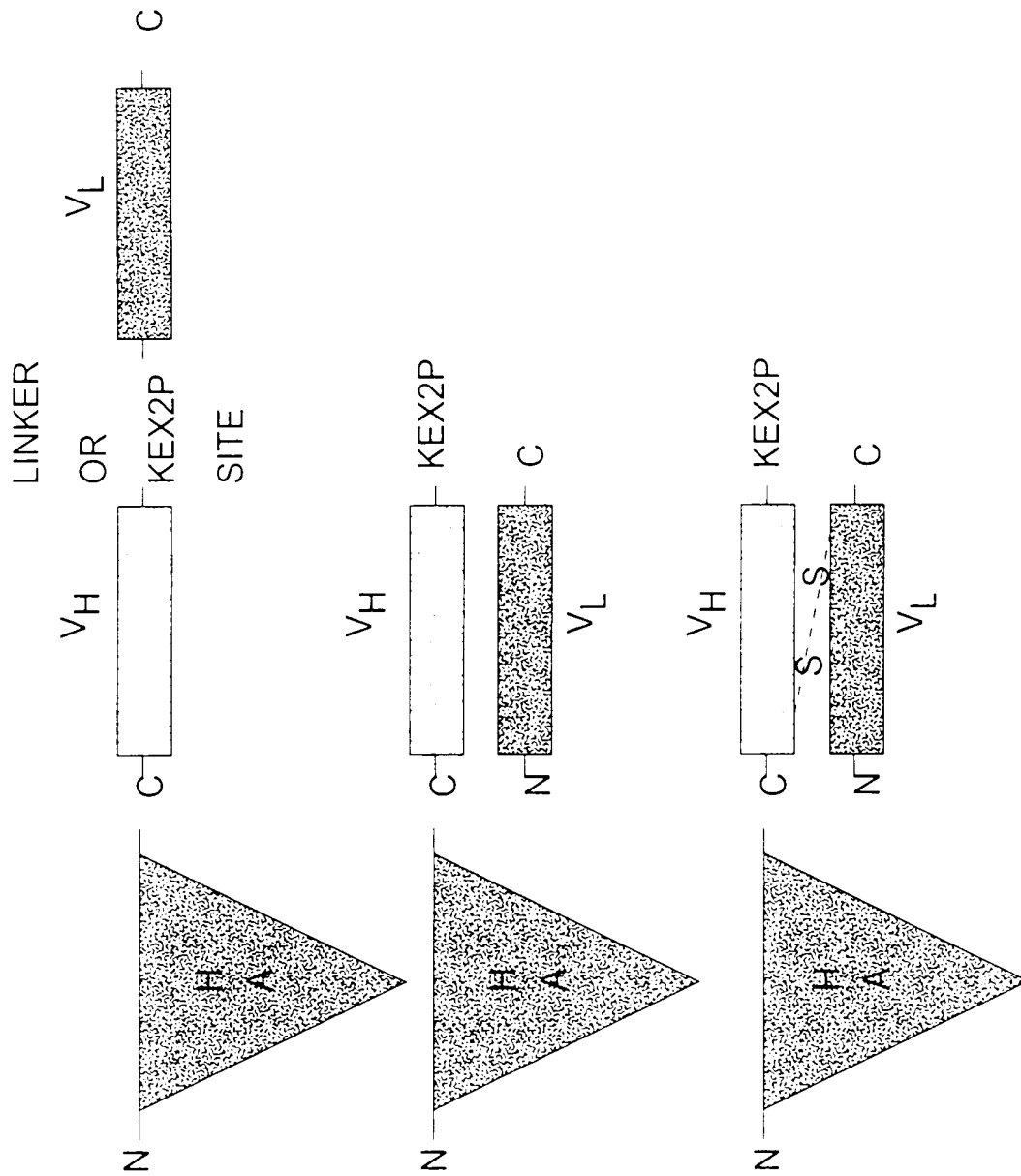FIG. 14

```
  1 GAT GCA CAC AAG AGT GAG GTT GCT CAT CGG TTT AAA GAT TTG GGA GAA GAA AAT TTC AAA  60
  1  D   A   H   K   S   E   V   A   H   R   F   K   D   L   G   E   E   N   F   K   20

 61 GCC TTG GTG TTG ATT GCC TTT GCT CAG TAT CTT CAG CAG TGT CCA TTT GAA GAT CAT GTA 120
 21  A   L   V   L   I   A   F   A   Q   Y   L   Q   Q   C   P   F   E   D   H   V   40

121 AAA TTA GTG AAT GAA GTA ACT GAA TTT GCA AAA ACA TGT GTT GCT GAT GAG TCA GTT GAA 180
 41  K   L   V   N   E   V   T   E   F   A   K   T   C   V   A   D   E   S   A   E   60

181 AAT TGT GAT AAA TCA CTT CAT ACC CTT TTT GGA GAC AAA TTA TGC ACA GTT GCA ACT CTT 240
 61  N   C   D   K   S   L   H   T   L   F   G   D   K   L   C   T   V   A   T   L   80

241 CGT GAA ACC TAT GGT GAA ATG GCT GAT TGT TGT GCA AAA CAA GAA CCT GAG AGA AAT GAA 300
 81  R   E   T   Y   G   E   M   A   D   C   C   A   K   Q   E   P   E   R   N   E  100

301 TGT TTC TTG CAA CAC AAA GAT GAC AAC CTC CCG GGA TTG GTG AGA CCA GAG GTT 360
101  C   F   L   Q   H   K   D   D   N   L   P   H   L   V   R   P   E   V  120

361 GAT GTG ATG TGT ACT GCT TTT CAT GAC AAT GAG ACA TTT TTG AAA AAA TAC TTA TAT 420
121  D   V   M   C   T   A   F   H   D   N   E   E   T   F   L   K   K   Y   L   Y  140

421 GAA ATT GCC AGA AGA CAT CCT TAC TTT TAT GCC CCG GAA CTC CTT TTT GCT AAA AGG 480
141  E   I   A   R   R   H   P   Y   F   Y   A   P   E   L   L   F   A   K   R  160
```

Figure 15A

```
481 TAT AAA GCT GCT TTT ACA GAA TGT TGC CAA GCT GCT GAT AAA GCC TGC CTG TTG CCA 540
161  Y   K   A   A   F   T   E   C   C   Q   A   A   D   K   A   A   C   L   L   P  180

541 AAG CTC GAT GAA CTT CGG GAT GAA GGG AAG GCT TCG TCT GCC AAA CAG AGA CTC AAA TGT 600
181  K   L   D   E   L   R   D   E   G   K   A   S   S   A   K   Q   R   L   K   C  200

601 GCC AGT CTC CAA AAA TTT GGA GAA AGA GCT TTC AAA GCA TGG GCA GTG GCT CGG CTG AGC 660
201  A   S   L   Q   K   F   G   E   R   A   F   K   A   W   A   V   A   R   L   S  220

661 CAG AGA TTT CCC AAA GCT GAG TTT GCA GAA GTT TCC AAG TTA GTG ACA GAT CTT ACC AAA 720
221  Q   R   F   P   K   A   E   F   A   E   V   S   K   L   V   T   D   L   T   K  240

721 GTC CAC ACG GAA TGC TGC CAT GGA GAT CTG CTT GAA TGT GCT GAT GAC AGG GTG GAC CTT 780
241  V   H   T   E   C   C   H   G   D   L   L   E   C   A   D   D   R   A   D   L  260

781 GCC AAG TAT ATC TGT GAA AAT CAG GAT TCG ATC TCC AGT AAA CTG AAG GAA TGC TGT GAA 840
261  A   K   Y   I   C   E   N   Q   D   S   I   S   S   K   L   K   E   C   C   E  280

841 AAA CCT CTG TTG GAA AAA TCC CAC TGC ATT GCC GAA GTG GAA AAT GAT GAG ATG CCT GCT 900
281  K   P   L   L   E   K   S   H   C   I   A   E   V   E   N   D   E   M   P   A  300

901 GAC TTG CCT TCA TTA GCT GCT GAT TTT GTT GAA AGT AAG GAT GTT TGC AAA AAC TAT GCT 960
301  D   L   P   S   L   A   A   D   F   V   E   S   K   D   V   C   K   N   Y   A  320
```

Figure 15B

```
 961 GAG GCA AAG GAT GTC TTC CTG GGC ATG TTT TTG TAT GAA TAT GCA AGA AGG CAT CCT GAT 1020
 321  E   A   K   D   V   F   L   G   M   F   L   Y   E   Y   A   R   R   H   P   D   340

1021 TAC TGT GTG GTG CTG CTG CTG AGA CTT GCC AAG ACA TAT GAA ACC ACT CTA GAG AAG TGC 1080
 341  Y   S   V   V   L   L   L   R   L   A   K   T   Y   E   T   T   L   E   K   C   360

1081 TGT GCC GCT GCA GAT CCT GAA CAT GAA TGC TAT GCC AAA GTG TTC GAT GAA TTT AAA CCT CTT 1140
 361  C   A   A   D   P   H   E   C   Y   A   K   V   F   D   E   F   K   P   L   380

1141 GTG GAA GAG CCT CAG AAT TTA ATC AAA AAC TGT GAG CTT TTT GAG CAG CTT GGA GAG 1200
 381  V   E   E   P   Q   N   L   I   K   Q   N   C   E   L   F   E   Q   L   G   E   400

1201 TAC AAA TTC CAG AAT GCG CTA TTA GTT TAC ACC AAG AAA GTA CCC CAA GTG TCA ACT 1260
 401  Y   K   F   Q   N   A   L   L   V   P   Y   T   K   K   V   P   Q   V   S   T   420

1261 CCA ACT CTT GTA GAG GTC TCA AGA AAC CTA GGA AAA GTG GGC AGC AAA TGT TGT AAA CAT 1320
 421  P   T   L   V   E   V   S   R   N   L   G   K   V   G   S   K   C   C   K   H   440

1321 CCT GAA GCA AAA AGA ATG CCC TGT GCA GAA GAC TAT CTA TCC GTG GTC CTG AAC CAG TTA 1380
 441  P   E   A   K   R   M   P   C   A   E   D   Y   L   S   V   V   L   N   Q   L   460

1381 TGT GTG TTG CAT GAG AAA ACG CCA GTA AGT GAC AGA GTC ACA AAA TGC TGC ACA GAG TCC 1440
 461  C   V   L   H   E   K   T   P   V   S   D   R   V   T   K   C   C   T   E   S   480
```

Figure 15C

```
1441 TTG GTG AAC AGG CGA CCA TGC TTT TCA GCT CTG GAA GTC GAT GAA ACA TAC GTT CCC AAA 1500
481   L   V   N   R   R   P   C   F   S   A   L   E   V   D   E   T   Y   V   P   K  500

1501 GAG TTT AAT GCT GAA ACA TTC ACC TTC CAT GCA GAT ATA TGC ACA CTT TCT GAG AAG GAG 1560
501   E   F   N   A   E   T   F   T   F   H   A   D   I   C   T   L   S   E   K   E  520

1561 AGA CAA ATC AAG AAA CAA ACT GCA CTT GTT GAG CTT GTG AAA CAC AAG CCC AAG GCA ACA 1620
521   R   Q   I   K   K   Q   T   A   L   V   E   L   V   K   H   K   P   K   A   T  540

1621 AAA GAG CAA CTG AAA GCT GTT ATG GAT GAT TTC GCA GCT TTT GTA GAG AAG TGC TGC AAG 1680
541   K   E   Q   L   K   A   V   M   D   D   F   A   A   F   V   E   K   C   C   K  560

1681 GCT GAC GAT AAG GAG ACC TGC TTT GCC GAG GAG GGT AAA AAA CTT GTT GCT GCA AGT CAA 1740
561   A   D   D   K   E   T   C   F   A   E   E   G   K   K   L   V   A   A   S   Q  580

1741 GCT GCC TTA GGC TTA TAA CAT CTA CAT TTA AAA GCA TCT CAG 1782
581   A   A   L   G   L   *                                   585
```

Figure 15D